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Report

Age Estimate of the N370S Mutation Causing Gaucher Disease in Ashkenazi Jews and European Populations: A Reappraisal of Haplotype Data

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Summary

The N370S mutation at the GBA locus on human chromosome 1q21, which causes Gaucher disease (GD), has a high frequency in the Ashkenazim and is the second-most-widespread GD mutation in the European non-Jewish population. A common ancient origin for the N370S mutation in the Ashkenazi Jewish and Spanish populations has been proposed on the basis of both a similar haplotype for associated markers and an age estimate that suggests that this mutation appeared several thousand years ago. However, a reappraisal of haplotype data, using the Risch formula properly along with a Luria-Delbrück setting of the genetic clock, allows identification of the likely origin of the N370S mutation in Ashkenazi Jews between the 11th and 13th centuries. This result is consistent with the estimated ages of other mutations that are frequent among Ashkenazim, with the exception of type II (Glu117Stop) factor XI deficiency, which is deemed to be >3000 years old, predating the separation of the Ashkenazi and Iraqi Jews. The present finding supports the hypothesis of a more recent origin for the N370S mutation and is consistent with both a founder chromosome transfer from Ashkenazim who assimilated in some European populations and a non-Jewish origin of the European N370S-bearing chromosomes.

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Gaucher disease (GD [MIM 230800, 230900, 231000]), first described >100 years ago by Philippe Gaucher in a 32-year-old woman with splenomegaly (Gaucher 1882), is the most common glycolipid storage disorder and is caused by a deficiency in the activity of the catabolic enzyme glucocerebrosidase (GBA: lysosomal acid β-glucosidase, E.C.3.2.1.45). The defective enzyme drives N-acyl-sphingosyl-1-*O*-β-D-glucoside to accumulate in macrophages throughout the patient's body. GD's mode of inheritance is autosomal recessive, and disease frequency is particularly high among Ashkenazi Jews (~1/500 live births vs. 1/60,000–1/360,000 in the white non-Jewish population). In Ashkenazim affected by GD, the N370S mutation in exon 9 of the GBA gene (cDNA 1226: 5841A→G; 370Asn→Ser) is by far the most common, representing >70% of GD mutations in Ashkenazi Jewish patients (Beutler et al. 1992), with a gene frequency in the population of ~.003. Linkage disequilibrium (LD) has been shown between the N370S mutation and the Pv1.1− haplotype, on the basis of the absence of a *Pvu*II restriction site in intron 6 of the GBA gene (Beutler et al. 1992). N370S is also the second-most-common GD mutation in European non-Jewish populations, with a high frequency among Portuguese and Spanish patients (Amaral et al. 1996; Cormand et al. 1998).

Recently, Cormand et al. (1997, 1998) finely mapped the GBA gene on chromosome 1q21 in relation to several highly polymorphic markers and identified a putative ancestral haplotype associated with the N370S mutation in chromosomes from Spanish patients. Díaz et al. (1999) extended this study to 66 unrelated Ashkenazi Jewish patients affected by GD and of central and eastern European descent, confronting their haplotypes for 1q markers, as well as those of 14 Spanish GD patients, with the corresponding haplotypes from Ashkenazi and

non-Jewish controls. In their otherwise interesting and potentially useful report, the authors made some erroneous calculations when they attempted to estimate the age of the N370S mutation among the Ashkenazi Jews, using LD analysis. The source of the error lies in the use of a wrong version of the formula (equation 1) by Risch et al. (1995*b,* p. 158). The typographical error (" × " should read "=") was never corrected through publication of an erratum, but apparently it was known to authors who later applied Risch et al.'s formula correctly (e.g., Moisio et al. 1996). However, Gou and Xiong (1997, p. 320), yielding a similar formula, had the opportunity to point out the misprint. Unfortunately, another error plagues the same erroneous equation in Díaz et al.'s article (1999): the argument of the logarithm on the numerator should be $1 - Q/(1 - p_N)$ and not $(1 - Q)/(1 - p_N)$. This second slip, altering considerably the value of the logarithm, prevented the authors from recognizing the original error, which would have been evident from the resulting unlikely high value of the estimated age of the mutation (i.e., the square of the expected age).

By use of data from Díaz et al. (1999) and application of the correct algorithm in the concise form

$$g = \log\delta/\log(1 - \theta), \qquad (1)$$

where δ is the LD measure originally defined by Bengtsson and Thomson (1981) as $(p_D - p_N)/(1 - p_N)$ and θ is the recombination fraction, the age of the N370S mutation at the GBA locus can be re-estimated from marker-allele frequencies and from the distance between the gene under examination and five highly polymorphic 1q markers for which LD was confirmed (table 1). Based on two assumed distances (0.025 and 0.037 cM) for D1S2624, the only marker in LD with the GBA locus for which θ is available from both meiotic and RH mapping, the estimate of the age of the N370S mutation in Ashkenazi Jews is 30–20 generations (750–500 years, if we assume 25 years/generation) and not 381–169 generations, as reported by Díaz et al. (1999). However, as suggested by Labuda et al. (1996, 1997), it is likely that the age estimated from equation (1) is an underestimate: attention has been drawn by these authors to "the fact that, when applied to growing populations, the genetic clock ticks more slowly than expected" (1997, p. 769). A straightforward approach to the problem (Labuda et al. 1996) is to set the genetic clock, according to the Luria-Delbrück correction (Luria and Delbrück 1943), as follows:

$$g_c = g + g_0, \qquad (2)$$

where g is the number of generations estimated from equation (1) and

$$g_0 = -(1/d)\ln(\theta f_d), \qquad (3)$$

f_d being equal to $e^d/(e^d - 1)$ in a population growing at a rate d (for small d values, $f_d \approx 1/d$). In our case, marker D1S2624 gives $g_0 = 6.5$ for $\theta = .025$ and $g_0 = 5.5$ for $\theta = .037$ (table 1) under the assumption that $d = .4$ (Risch et al. 1995*a;* Labuda et al. 1997). Use of this correction shifts the rough dating of the genomic founder event for the N370S mutation GD in the Ashkenazi Jewish population back by almost 1.5 centuries. Thus, contrary to Díaz et al.'s (1999) estimate (several thousand years BC), the founder effect could have started as late as the first half of the second millennium AD.

Estimation of the age of the Ashkenazim's most common GBA mutation by a genetic-clock–derived equation is subject to two sources of errors. As noted by Díaz et al. (1999), the first is due to the uncertainty in the RH and meiotic estimates of θ, RH generally yielding greater distances between marker loci than does meiotic mapping (Moisio et al. 1996). To reduce this effect, the authors used both recombination and RH data, when available, providing an interval for the number of generations (g) since the appearance of the mutation. Improved results may be expected when gene-marker distances from finer integrated maps of chromosome 1q are available. The second source of error is due to the fact that LD analysis based on haplotype frequencies is sensitive to sampling phenomena, and statistical fluctuation resulting from sampling variance is difficult to calculate (Risch et al. 1995*b*). Furthermore, the estimated age of the mutation tends to vary considerably from marker to marker. This is probably due to sampling variations in allele frequencies and to the uncertainty intrinsic to the age estimate. However, the exact reason for the observed discrepancies is unknown and warrants further investigation.

Age estimates of a few mutant alleles at loci involved in autosomal diseases of high frequency in the Ashkenazim, as well as of a BRCA1 mutation (185delAG) present in this population, are obtainable from data reported in the recent literature (table 2). With the notable exception of one of the two major mutations causing factor XI deficiency (Glu117Stop), which is common to Ashkenazi Jews, non-Ashkenazi (Iraqi) Jews, and Arabs and is supposed to be >2000 (Peretz et al. 1997) or 3000 (Goldstein et al. 1999) years old, the origin of investigated disease-linked alleles can be dated between the 11th and 13th centuries. Use of the Luria-Delbrück setting of the genetic clock, as suggested by Labuda et al. (1996, 1997), shifts the original dating of Bloom syndrome, familial dysautonomia, and idiopathic torsion dystonia mutations back by 150–200 years. The corrected estimated age of N370S mutation at the GBA locus (~635–900 years) suggests that the origin of the founder effect occurred at the beginning of our millen-

Table 1

Haplotype, LD Analysis, and Corrected Estimated Age of the N370S (5841A→G) Mutation in Chromosome 1q21 of Ashkenazi Jewish Patients

							Estimated Age			
		Distance[a]	LD Analysis[b]				Generations[c]			
Marker	Allele	(θ)	p_d	p_n	χ^2 (P value)	δ	g	g_0	g_c	Years[d]
D1S305	1	.024[e]	.586	.400	5.2 (<.5)	NS	…	…	…	…
		.023[f]	.586	.400	5.2 (<.5)	NS	…	…	…	…
D1S2140	4	.022	.956	.475	49.6 (<.001)	.92	3.9	6.8	10.7	268
D1S2777	1	.011	.978	.638	33.3 (<.001)	.94	5.7	8.5	14.2	355
D1S1595	5	.024	.938	.450	43.7 (<.001)	.87	5.8	6.5	12.3	308
D1S2721	3	.030	.936	.338	69.1 (<.001)	.90	2.9	6.0	8.9	223
D1S2624	4	.037[e]	.578	.200	70.0 (<.001)	.47	19.9	5.5	25.4	635
		.025[f]	.578	.200	70.0 (<.001)	.47	29.6	6.5	36.1	903

Note.—NS = not significant.

[a] Data from Cormand et al. (1997) and Díaz et al. (1999).

[b] Data from Díaz et al. (1999).

[c] Estimated by equations (1), (3), and (2), respectively (see text).

[d] Calculated with the assumption of 25 years/generation.

[e] Obtained from the Stanford G3 RH panel (Research Genetics), with the assumptions of 1cR/50 kb (Moisio et al. 1996) and 900 kb/1 cM.

[f] Obtained from meiotic mapping (Cormand et al. 1997).

nium, before or near the early 13th century, and is consistent with the results above. Such dating precedes the time of early migrations of Jews from Ashkenaz (medieval Germany) to European countries (Barnavi 1992; Beirnart 1992). However, as suggested by likelihood studies (Kaplan et al. 1995), it should be noted that the Luria-Delbrück correction may be conservative (i.e., $g + g_0$ underestimates the true age); under this assumption, the founder effect would be older rather than younger. In any case, the age estimate is consistent with a historically plausible scenario in which a founder effect originated in a small group of successful Jewish migrants that underwent a demographic expansion (Labuda et al. 1997). Robust evidence supporting the founder-effect hypothesis to explain the high frequency of the N360S mutation observed in Ashkenazi Jews comes from strong LD with specific alleles at adjacent genetic loci. It has previously been shown (Beutler et al. 1992) that the Pv1.1− haplotype on the GBA gene itself is in complete LD with the N360S mutation. However, since both Pv1.1− and Pv1.1+ are common polymorphisms, two or more independent mutational events in nucleotide 1226 of the GBA genomic sequence could have occurred on the same haplotype in different chromosomes 1q21 at different times. More recently, a trinucleotide-repeat polymorphism (eight alleles) was reported for the liver-type pyruvate kinase (PKRL) gene (Lenzner et al. 1994), which is closely linked to the GBA locus (Glenn et al. 1994; Cormand et al. 1997). The new marker locus enabled Rockah et al. (1998) to refine GD haplotype analysis. The degree of LD (δ) between the N360S mutation and the A1 allele of the PKRL gene, which is relatively uncommon (7%) in Ashkenazi Jewish chromosomes, was found to be .957. This result strongly suggests that the mutation originated in a single founder chromosome, thus supporting the conclusion drawn by Beutler et al. (1992). Moreover, it has been noted (Rockah et al. 1998) that, since GBA and PKRL are very tightly linked (<.2 cM), the deviation from complete LD ($1 - \delta = .043$) "may reflect slippage at the repetitive site in the PKRL gene, rather than *bona fide* recombination between the two loci" (p. 235).

In conclusion, the above-mentioned evidence supports a founder effect for the N360S mutation in Ashkenazi Jews. Nevertheless, it does not unambiguously contribute to either the hypothesis of a genetic drift associated with the remarkable expansion of this population in Europe during the 16th–19th centuries (Goodman 1978) or the hypothesis of a selective advantage of heterozygotes over noncarriers (Gravel et al. 1995) to explain the present mutant allele's high frequency. As suggested by Goldstein et al. (1999) for the type II (Glu117Stop) mutation causing factor XI deficiency in both Iraqi and Ashkenazi Jews, these two possibilities may ultimately be distinguishable by a comparison of the shape of the affected chromosomes with those of the genealogies of supposedly selectively neutral genomic regions. The present re-estimation of the age of the N360S mutation in Ashkenazi Jews does not settle the question of whether the mutation originated in the primitive Ashkenazi Jewish community (9th–13th centuries), spreading later to various European populations by occasional intermarriage, or whether it was an original European mutation introduced into the Ashkenazi Jewish population in the

Table 2

Estimated Dates of Origin of Mutations Causing Diseases among Ashkenazi Jews

Disease	MIM	Locus	Mutation	Linked Marker	Allele	Distance (θ)	LD (δ)	Estimated Age[a]			Year of Origin[b]	Data Source
								g	g_0	g_c		
Bloom syndrome	210900	15q26.1	Blm(Ash)	FES	C3	.012	.803	18	8	26	~1300	Ellis et al. 1994
Factor XI deficiency	264900	4q35	Glu117Stop (type II)	…	…	…	…	…	…	…	≤586 BC–70 AD[g]	Peretz et al. 1997
				D4S171	151	.013	.161	120[c]			≤1000 BC	Goldstein et al. 1999
					153		.064	189[c]				
			Phe283Leu (type III)	D4S171	145/151	.013	.627	31[c]	…	…	≤1180	Goldstein et al. 1999
Familial dysautonomia	223900	9q31	DYS[d]	D9S105	8	.036[e]	.427	23	6	29	~1230	Blumenfeld et al. 1993, 1999
Idiopathic torsion dystonia	128100	9q34	DYT1[AJ]	D9S64	2/10	.023	.556	25	7	32	~1150	Risch et al. 1995*b*
Breast-ovarian cancer	113705	17q21	BRCA1	D17S1327	…	…	…	38[f]	…	…	~1000	Neuhausen et al. 1996
			185delAG	et al.							(330–1670)	

[a] No. of generations. Unless otherwise stated, g values were estimated by means of equation (3) or an equivalent formula (see text); g_0 and g_c were obtained according to Labuda et al. 1996.

[b] A conversion factor of 25 years/generation and an average year of birth of 1950 for all affected and carrier subjects were assumed.

[c] Estimate of the coalescent time of disease chromosomes (Reich and Goldstein 1999).

[d] Gene not cloned.

[e] The original θ value (.030: Blumenfeld et al. 1993) has been refined by use of the more precise genetic mapping of DYS (Blumenfeld et al. 1999).

[f] Value obtained by means of a maximum-likelihood method for multipoint haplotype data.

[g] Based on historical consideration of the time that elapsed between the destruction of the First and the Second Temples in Jerusalem.

same way. Moreover, there are no data supporting one of the two hypotheses of Díaz et al. (1999) on the N370S origin, that the mutation may have been introduced by an ancient Jewish founder several thousand years ago, before the divergence of Ashkenazi and non-Ashkenazi Jewish populations.

Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for GD [MIM 230800, 230900, and 231000])

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